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INSTITUTE OF MEDICINE

Shaping the Future for Health

THE ANTHRAX VACCINE: IS IT SAFE? DOES IT WORK?

In autumn of 2001, anthrax emerged as a national concern. Deliberate distribution through the mail of anthrax bacteria led to at least five deaths and 13 nonfatal infections. Thousands of people received treatment for known or suspected exposure to the bacteria.

An Institute of Medicine (IOM) study already under way on the vaccine now used to protect humans against anthrax, called Anthrax Vaccine Adsorbed, was accelerated in response to these events. The IOM issued its report—*The Anthrax Vaccine: Does It Work? Is It Safe?*—in March 2002.

HOW DO PEOPLE GET ANTHRAX?

Anthrax is caused by bacteria that are usually confined to animals such as cows and sheep. Historically, humans have gotten the disease through contact with animals or animal products, such as hair or hides, that are contaminated with anthrax "spores." These spores, which are dormant forms of the bacteria, can exist in the environment for years. If a person takes in spores—perhaps by breathing or through a cut in the skin—the spores can then germinate into active bacteria that produce powerful poisons.

Major concern now centers on the possibility that terrorists or a hostile nation might use "bioweapons" to expose large numbers of people—soldiers or civilians—to anthrax spores. What makes anthrax attractive for such use is that its spores can be processed into a form (such as the "white powder" circulated in ordinary envelopes sent through the mail) that can readily become airborne and spread across fairly wide areas. Anyone exposed to the spores will be at risk of developing anthrax.

The IOM report concludes that the vaccine is effective in protecting humans against anthrax.

DOES THE VACCINE WORK?

The IOM report concludes that the vaccine is effective in protecting humans against anthrax. The vaccine is administered in a series of six subcutaneous (under the skin) injections. After the initial dose, shots are given at 2 weeks, 4 weeks, 6 months, 12 months, and 18 months. Annual booster shots are required.

Why this happens is not known, but may be due to such factors as differences in body mass or care-seeking behavior.

- ***The Department of Defense should speed up its research to develop an improved vaccine.*** A new vaccine should not cause any severe local reactions, should require only two or three injections that provide protection for at least a year, and should remain potent for a long period of time so that it can be stockpiled to ensure ample supplies when needed.

WHAT PROMPTED THE IOM STUDY?

The vaccine was approved by the government in 1970. It was first used on a limited basis, primarily to protect people who might be exposed to anthrax spores where they worked, such as veterinarians and textile plant workers who process animal hair. In 1991, its use expanded greatly. The U.S. military, worried that Iraq possessed anthrax bioweapons, administered the vaccine to some 150,000 service members deployed for the Gulf War. When it later became clear that Iraq had indeed developed anthrax bioweapons, the Department of Defense announced a plan for the mandatory vaccination of all U.S. service members. The Anthrax Vaccine Immunization Program began in March 1998 with personnel sent to high-risk areas, such as South Korea and Southwest Asia.

As more service members received the vaccine, however, some of them raised concerns about how well it works and how safe it is. Some service members also suggested that the vaccine might have caused the illnesses experienced by some Gulf War veterans. In addition, problems arose with manufacture of the vaccine. In early 1998, the only company making the vaccine closed its facility for renovation. The company resumed limited production in 1999, but the Food and Drug Administration prohibited the release of any newly produced vaccine until the company demonstrated that its production process met all federal regulations. Following the halt in production, supplies of the vaccine dwindled, and by 2000 the military had extensively slowed its vaccination program.

In response to these concerns, Congress directed the Department of Defense to support an independent examination of the vaccine. In October 2000, the Institute of Medicine convened the Committee to Assess the Safety and Efficacy of the Anthrax Vaccine to carry out this study. Recognizing that it was dealing with difficult and controversial issues, the committee chose to be as open as possible, electing to hear from all groups and individuals who wished to contribute data, concerns, or complaints. The committee prepared its report after considering all available evidence.

The bottom line: the vaccine will be produced under strict controls according to current federal requirements.

IS MORE VACCINE BEING MADE?

The vaccine manufacturer received government approval of to release newly-produced vaccine in January 2002, and it plans to begin shipping new supplies in the near future.

As part of its study, the IOM committee reviewed and evaluated the steps taken by the company to gain approval. The bottom line: the vaccine will be produced under strict controls according to current federal requirements.

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TABLE 6-4 Record-Linkage Studies of Adverse Events Following Anthrax Vaccination

Study	Study Population and Observation Period	Data Collection Method(s)	Number
Single-Service Databases			
Air Combat Command Study (Rehme, 2001; Rehme et al., 2002)	Air Force personnel with medical visit during 1998 deployment in SWA, 1998–1999	Air Force and DoD databases on vaccination and postdeployment health care visits	5,177 per
Men			4,352
Women			825
Army Aviation Epidemiology Register (Mason et al., submitted for publication)	Army aircrew personnel; Jan. 1998–Nov. 2000	Records from aviation physical examinations conducted within 24 months before and after vaccination	3,356 ma vaccinate unvaccina personnel
DoD Databases			
Naval Health Research Center analysis (Sato, 2001a,b; Sato et al., 2001)	All personnel on active duty; Jan. 1, 1998–March 31, 2000	DoD records on hospitalization in military or civilian facilities linked to DoD records on vaccination and personnel data	Vaccinate 2,651 h 120,870 Unvaccin 151,609 2.3 mill

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:thod(s)	Number of Subjects	Findings
iation and ilth care	5,177 persons	No significant increase in risk for use of ambulatory care or for any specific diagnosis
		Selected results as relative risk (vaccinated versus unvaccinated; 95% CI) Any postdeployment outpatient visit: 0.96 (0.90–1.02) Muscle aches: 0.75 (0.41–1.35) Migraine: 0.93 (0.38–2.32) Hearing loss: 0.28 (0.08–0.97) Diabetes: 1.68 (0.20–13.9) Sleep disorders: 2.80 (0.36–21.9) Tinnitus: 0.42 (0.07–2.51)
	4,352	Any postdeployment outpatient visit: 0.95 (0.88–1.02)
	825	Any postdeployment outpatient visit: 0.99 (0.88–1.12)
ion ins 4 months :cination	3,356 matched pairs of vaccinated and unvaccinated aircrew personnel	No significant increase in risk for any outcome Selected results as odds ratio (vaccinated versus unvaccinated; 95% CI) Weight change (>19 lbs [8.6 kg]): 0.61 (0.45–0.83) Intraocular pressure >20 mm Hg: 0.40 (0.13–1.28) Hearing loss >15 dB: 0.94 (0.82–1.08) Diabetes or fasting blood sugar >115 mg/dL: 1.25 (0.34–4.66)
ilitary linked	Vaccinated: 2,651 hospitalizations 120,870 person-years	Risk for hospitalization within 42 days of vaccination for any of 14 summary ICD-9-CM diagnostic categories is significantly lower for vaccinated men and women
sonnel data	Unvaccinated: 151,609 hospitalizations 2.3 million person-years	Range for adjusted relative risk (vaccinated versus unvaccinated; 95% CI) Men: 0.30 (0.27–0.33) to 0.75 (0.68–0.84) Women: 0.17 (0.11–0.26) to 0.67 (0.47–0.94)

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TABLE 6-4 Continued

Study	Study Population and Observation Period	Data Collection Method(s)	Number
Army Medical Surveillance Activity DMSS analyses (AMSA, 2001a,b,c)		DMSS records on inpatient and outpatient visits and on vaccination history	
Screening analyses	All personnel on active duty; Jan. 1, 1998–Dec. 31, 2000		Vaccinate 757,54(Unvaccin 3.4 mill
Hypothesis testing analyses	All personnel on active duty; Jan. 1, 1998–Dec. 31, 2000		Vaccinate 515,38(Unvaccin 2.8 mill
Post- versus prevaccination hospitalization	Vaccinated personnel only, Jan. 1, 1998–Dec. 31, 2000		Postvacci 738,38 Prevaccin 478,09
Post- versus prevaccination hospitalization; at 0–45 days and >45 days postvaccination	Vaccinated personnel only, Jan. 1, 1998–Dec. 31, 2000		Postvacci 0–45 da person->45 day person- Prevaccin 478,09

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:thod(s)	Number of Subjects	Findings
ıpatient s and ɔry		See Appendix G for a complete listing of all significantly elevated adjusted rate ratios (RR) from these analyses
	Vaccinated: 757,540 person-years Unvaccinated: 3.4 million person-years	No significant elevation of risk among vaccinated personnel for inpatient, outpatient, or incident visits for any of 14 summary ICD-9-CM diagnostic categories
	Vaccinated: 515,389 person-years Unvaccinated: 2.8 million person-years	No significant elevation of risk among vaccinated personnel for any of 12 inpatient and 14 outpatient diagnoses
	Postvaccination: 738,382 person-years Prevaccination: 478,093 person-years	Of 843 diagnoses, adjusted RR significantly lowered for 12 diagnoses and significantly elevated for 15 (see Appendix G, Table G-1). Diagnoses with significantly elevated adjusted RR (95% CI) include Inguinial hernia (ICD-9-CM 550): 1.31 (1.01–1.65) Diabetes mellitus (ICD-9-CM 250): 3.46 (1.51–7.90) Carcinoma in situ of breast and genitourinary system (ICD-9-CM 233): 5.14 (1.81–14.57)
	Postvaccination: 0–45 days: 165,682 person-years >45 days: 572,700 person-years Prevaccination: 478,093 person-years	For 0-45 days postvaccination: of 843 diagnoses, adjusted RR significantly lowered for 7 diagnoses and significantly elevated for 13 (see Appendix G, Table G-2). Diagnoses with significantly elevated adjusted RR (95% CI) include Diabetes mellitus (ICD-9-CM 250): 3.49 (1.39–8.79) Other disorders of the intestine (ICD-9-CM 569): 4.16 (1.51–11.49) For >45 days postvaccination: of 843 diagnoses, adjusted RR were significantly lowered for 10 diagnoses and significantly elevated for 20 (see Appendix G, Table G-2). Diagnoses with significantly elevated adjusted RR (95% CI) include Diabetes mellitus (ICD-9-CM 250): 3.44 (1.47–8.06) Other disorders of the intestine (ICD-9-CM 569): 2.61 (1.06–6.44)

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differences in deployment status. Although analyses were statistically adjusted for quartiles of number of days deployed, this approach may not have been adequate to fully control for differences between deployed and undeployed military personnel in their underlying health status or in the manner in which health-related issues are addressed for predeployment personnel. Also affecting the interpretation of the current results is the possibility that the disease categories used may be too broad to detect increases in risks of individual diseases in the group vaccinated with AVA.

AMSA Analyses of DMSS Data Regarding Health Outcomes Following Vaccination Against Anthrax

In 2000 and 2001, AMSA prepared several reports that described analyses that were carried out with data available from DMSS to assess whether inpatient or outpatient medical visits are associated with vaccination with AVA. AMSA also carried out analyses in response to specific questions raised by the IOM committee. As a result, several different approaches to the analyses of the data available from DMSS were taken over the course of the committee's work. Each is described separately.

Screening Analyses In 2001, AMSA began a process of regularly using DMSS data for screening purposes. It has since produced two quarterly reports describing screening analyses of data available from DMSS and DoD's electronic immunization tracking system database (AMSA, 2001a,b). The databases were used to compare rates of hospitalization and outpatient visits between military personnel who had and those had not been vaccinated against anthrax on the basis of 14 major disease categories and 824 specific diagnoses (identified on the basis of three-digit ICD-9-CM codes). A third analysis on incident visits (first visits for a diagnosis) to inpatient or outpatient facilities was also conducted. For the April 2001 quarterly report on data for January 1998 to December 2000, a total of 757,540 person-years of observation for the group that had received AVA and 3,430,459 person-years of observation for the group that had not received AVA were included in the analyses.

The analyses found that, for all major diagnostic categories, crude and adjusted rates of hospitalization and of outpatient visits and incident visits (incident visits include inpatient and outpatient visits combined) were lower in the group that received AVA than in the cohort that did not. For specific diagnoses within each database (hospitalization, outpatient, and incident data; a total of 2,472 comparisons), however, the rates of some diagnoses were statistically significantly higher for the group that received AVA than for the group that did not. In many cases, these diagnoses (e.g., malaria, wounds, and trauma) were ones that are expected to occur at higher rates in

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service members deployed overseas than in those remaining in the United States. Since personnel receiving the anthrax vaccine were those most likely to be deployed to areas where risks of exposure to infectious disease are higher, these statistical associations do not raise questions for further analysis. Statistically significant elevations in rates for outpatient visits were also found for certain malignant neoplasms, portal vein thrombosis, and acute pulmonary heart disease, among others. These statistical associations can raise hypotheses to be tested further in additional analyses, such as those described in the sections that follow to try to account for the healthy soldier effect. AMSA plans to continue these screening analyses as additional data accrue.

Hypothesis Testing Analyses AMSA also presented data to the committee to address specific concerns that had been raised regarding AVA (Lange et al., 2001a). As described above, the analyses compared rates of hospitalization and of outpatient visits for selected conditions among active-duty personnel who received one or more doses of AVA with the rates among those who had not yet been given AVA or who had never received AVA. Rate ratios were adjusted for differences between AVA recipients and AVA nonrecipients in terms of age, sex, rank, deployment, service, ethnicity, previous hospitalizations, calendar year, and occupation. Separate analyses for men and women were also done. Both the group that had received AVA and the group that had not received AVA could have received other types of vaccines.

Rates were calculated for the interval from January 1998 to June 2000 and included 515,389 person-years of observation for the group vaccinated with AVA and 2,873,751 person-years of observation for the group not vaccinated with AVA. The 12 inpatient and the 14 outpatient diagnoses selected for comparison were those for which concern in relation to AVA exposure had been publicly expressed or those that have been investigated in association with other vaccines. Inpatient conditions included arthropathies, asthma, connective tissue diseases, diabetes mellitus, Guillain-Barré syndrome, cardiac dysrhythmias, multiple sclerosis, thyroid disorders, and lymphatic cancers. Outpatient conditions included circulatory problems; endocrine or immunological conditions; genitourinary problems; connective tissue diseases; ill-defined conditions; and respiratory, skin, and nervous system diseases.

For each of the diagnostic categories examined, both the unadjusted and the adjusted rate ratios for hospitalization or outpatient visit rates for the group that received AVA compared with those for the group that did not receive AVA did not differ significantly from 1.0 (the ratio observed when the rates are equal). The rate ratios were less than 1.0 for nearly all of the diagnoses examined (ranges, 0.67 to 1.11 for hospitalizations and 0.68

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to 0.84 for outpatient conditions), indicating lower hospitalization and outpatient visit rates in the group that received AVA than in the group that did not receive AVA. Lower rates in the group that received AVA were observed for all personnel combined and for the separate analyses among male and female soldiers.

These data indicate that there was no excess risk of selected adverse health events that required either hospitalization or an outpatient visit among active-duty military personnel receiving AVA over a 2.5-year period. In fact, the group that received AVA tended to have fewer hospitalizations or outpatient visits than the group that did not receive AVA.

Inferences about the safety of AVA based on these hypothesis-testing data are limited for several reasons. First, only selected diagnoses were examined, and thus the analyses do not address all possible risks. In addition, many of the diagnostic categories subsumed multiple medical conditions. Thus, risks associated with specific conditions within these categories might have been missed. Although deployment status was included as a covariate in the adjusted rate ratio analyses, this approach may not have been sufficient to account for the many differences in health status and reporting biases for those who are eligible for deployment and those who are not eligible for deployment.

Subsequent Analyses to Address the Healthy Soldier Effect To address concerns about inherent health-related differences in personnel who did and did not receive AVA because of deployment and to examine a wider range of diagnoses, in response to the committee's request, a second set of analyses were performed with the DMSS data (AMSA, 2001c). Again, several approaches were used, and in most of these analyses, service members served as their own controls. Tables are found in Appendix G.

Postimmunization Versus Preimmunization Analyses: Overall Analyses In the first analysis, the hospitalization rates in the time period after the receipt of one or more doses of AVA were compared with the rates in the period before the receipt of AVA for the population of service members who had received at least one dose of AVA. The analyses included the active-duty personnel who had received one or more doses of AVA between January 1, 1998, and December 31, 2000. Pre- and postimmunization cohorts were established on the basis of each individual's daily immunization status during that time frame. Therefore each individual could contribute a different amount of preimmunization time depending upon his or her time in the military prior to receiving AVA. Rate ratios (the rate after vaccination with AVA versus the rate before vaccination with AVA) were calculated for hospitalizations for 843 specific diagnoses (identified on the basis of three-digit ICD-9-CM codes) and were adjusted by Poisson regres-

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sion methods for up to 11 covariates. Ratios were calculated only for diagnoses with at least five hospitalizations in each comparison group.

The results of these analyses were based on 11,436 hospitalizations during 478,093 person-years of observation in the preimmunization time period (crude rate, 23.92 per 1,000 person-years) and 21,436 hospitalizations during 738,382 years of observation in the postimmunization time period (crude rate, 29.03 per 1,000 person-years). The unadjusted overall rate ratio (the rate after vaccination with AVA versus the rate before vaccination with AVA) for hospitalization was 1.21. Hospitalization rates in the period after vaccination with AVA were higher than those in the period before vaccination for about one-half (414 of 843) of the diagnoses and were lower than those in the period before vaccination for the others. Of the conditions with rate ratios significantly different from 1.0, hospitalization rates in the period after vaccination were statistically significantly elevated for 15 conditions (see Appendix G, Table G-1) and were statistically significantly reduced for 12 conditions. One would have expected rates for about 42 diagnoses to be significantly different in the intervals before and after vaccination with AVA just by chance, given the large number of conditions examined. The significantly elevated rate ratios ranged from 1.31 (95 percent CI = 1.04 to 1.65) for inguinal hernia (ICD-9-CM code 550) to 5.14 (95 percent CI = 1.81 to 14.57) for carcinoma in situ of the breast and genitourinary system (ICD-9-CM code 233). The rate of hospitalization for diabetes mellitus was increased 3.46-fold (95 percent CI = 1.51 to 7.90) in the interval after vaccination with AVA.

Comparison of rates of hospitalization in the same individual before and after the receipt of AVA removes many of the biases inherent in comparing groups vaccinated with AVA and groups not vaccinated with AVA. However, one limitation of comparisons based on a single individual is that for very serious medical conditions (e.g., aplastic anemia or multiple sclerosis) the interval before vaccination with AVA will by definition have few or no events, since if such events had occurred, the soldier would likely never have been eligible to receive AVA.

Similarly, for a diagnosis generally made on an outpatient basis, such as diabetes, it is possible for the rate before vaccination with AVA to be artificially and differentially lower since those who had the disease and who had been hospitalized for it would be less likely to be deployed and therefore less likely to be vaccinated. A normal rate of hospitalization for the disease after vaccination would then appear to be an increase over the rate before vaccination, thus explaining the higher rate after vaccination with AVA without indicating that the vaccine caused the problem (particularly in the instance when that rate after vaccination with AVA remains below the expected rate for the population). In other words, the frequency of diabetes after receipt of AVA may appear to be elevated only because the

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rate in the time period before vaccination is especially low due to the healthy soldier effect. Whether this phenomenon explains the apparent higher risk after vaccination with AVA can be determined by comparing the rate before vaccination with AVA with the rate in those who never received AVA. If the rate before vaccination with AVA is significantly lower than that in those who were never vaccinated (as it is in the case of diabetes), it supports the conclusion that there is no increased risk attributable to AVA.

Postimmunization Versus Preimmunization Analyses by Time Window A second, similar analysis compared hospitalization rates for the same individuals for the period before immunization with AVA and two time periods after immunization: 0 to 45 days and more than 45 days. This analysis was intended to determine whether any excess risks following exposure to AVA might have been obscured in the previous analysis, which used a longer, open-ended postvaccination time frame. The approach to the analysis was the same as that described above, except that the period after immunization was divided into two time intervals. The unadjusted overall hospitalization rate ratio for the first time interval (0 to 45 days postvaccination versus prevaccination) was 1.08 (25.81 versus 23.92 per 1,000 person-years) and that for the second time interval was 1.25 (29.96 versus 23.92 per 1,000 person-years). Compared with the hospitalization rates before receipt of AVA, rates of hospitalization within 45 days of being given AVA were significantly greater than 1.0 for 13 of the 843 diagnoses examined (Appendix G, Table G-2) and significantly less than 1.0 for 7 diagnoses. Diagnoses for which adjusted rate ratios were statistically significantly greater than 1.0 included diabetes mellitus (adjusted rate ratio = 3.49, 95 percent CI = 1.39 to 8.79) and other disorders of the intestine (ICD-9-CM code 569; adjusted rate ratio = 4.16, 95 percent CI = 1.51 to 11.49). Most of the significantly elevated rate ratios in the first time period were associated with nonspecific diagnostic categories, such as other and unspecified disorders of the back (ICD-9-CM code 724). Given the number of diagnoses examined, significantly elevated rate ratios would have been expected for approximately 42 diagnostic categories just by chance.

In the second time interval (>45 days after vaccination with AVA), adjusted rate ratios for hospitalization were significantly greater than 1.0 for 20 of the diagnoses examined (Appendix G, Table G-2), including ratios of 3.44 (95 percent CI = 1.47 to 8.06) for diabetes mellitus and 2.61 (95 percent CI = 1.06 to 6.44) for other disorders of the intestine (ICD-9-CM code 569). Adjusted rate ratios significantly less than 1.0 were observed for 10 of the 843 diagnoses examined. No consistent pattern was observed when rate ratios for the first interval (0 to 45 days postimmunization) were compared with those for the second interval (>45 days postimmunization). That is, ratios were not uniformly either larger or smaller in the first inter-

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six were 7.60 and 3.25 per 100,000 population in the cohort that received one to three doses and the cohort that received four or more doses, respectively. The corresponding rate for those who never received AVA was 3.5/100,000 population. Thus, the rates of hospitalization for multiple sclerosis were similar in those receiving the greater number of AVA doses and in persons who had never been immunized with AVA.

It is also noteworthy, as mentioned earlier, that the prevaccination disease history of service members who received AVA because they were going to be deployed will, by definition, not include any severe, chronic conditions that would have disqualified them from deployment. For nearly all diagnostic groups, hospitalization rate ratios were smaller rather than larger for the higher-dose cohort. Thus, no dose-response effects of AVA and the risk of hospitalization were observed. A dose-response effect may not be observed, however, if persons with significant health conditions that required hospitalization, whether or not these conditions occurred in conjunction with exposure to AVA, did not receive additional doses of the vaccine. If this were the case, even in the presence of a true association, higher risk ratios would be expected for the cohort that received one to three doses.

Preimmunization Versus Nonimmunization Analyses The fourth analysis was somewhat different from the first three in that hospitalization rates in the time period before vaccination with AVA for those ultimately vaccinated were compared with the rates for those who were never vaccinated with AVA. This comparison would allow assessment of inherent differences in disease risk among those who received AVA at some time and those who never did. The results of these analyses were based on 11,436 hospitalizations during 478,093 person-years of observation in the cohort evaluated before immunization (crude rate, 23.92 per 1,000 person-years) and 109,893 hospitalizations during 2,890,037 person-years of observation in the cohort that was never immunized (crude rate, 38.02 per 1,000 person-years). The unadjusted overall rate ratio for hospitalization (preimmunization versus never immunized) was 0.63. The rate ratios for all major categories but one (diseases of the skin; adjusted rate ratio = 1.01) were less than 1.0, as would be expected if those who would receive AVA were healthier than those who never received AVA. These rate ratios ranged from 0.29 to 0.91, indicating for many conditions a substantial healthy soldier effect. Hospitalization rates for specific diagnoses of diabetes mellitus, regional enteritis, other disorders of the intestine, and multiple sclerosis were also significantly lower in the preimmunization cohort (rates provided in the interpretation section below). For five diagnoses (malaria; erythematous conditions; superficial injury of elbow, forearm, and wrist; toxic effect of carbon monoxide; and effects of air pressure), hospitalization rates were

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statistically significantly higher for the preimmunization cohort than in those never immunized (Appendix G, Table G-4). Overall, the results of these analyses confirm that those who ultimately received AVA were healthier as a group, even before receipt of the vaccine, than those who never received AVA.

Postimmunization Versus Preimmunization Analyses, Including Those Unvaccinated The final analyses, done separately for men and women, compared the rates of hospitalization for specific diagnoses during the period before receipt of AVA with the rates after receipt of the first dose of AVA. The population included all personnel on active duty between January 1, 1998, and December 31, 2000. In this comparison, the rates for the preimmunization cohort were based on those for all active-duty personnel, including those who never received AVA, whereas the postimmunization time period covered the interval after receipt of the first dose of AVA among those who were vaccinated. Twelve specific diagnoses were investigated: arthropathies and related disorders; asthma; diffuse disease of connective tissue; diabetes mellitus; disease of the ear and mastoid process; inflammatory and toxic neuropathy; cardiac dysrhythmias; lymphosarcoma and reticulosarcoma; multiple sclerosis; acute myocardial infarction; disorders of the thyroid gland; and diseases of the esophagus, stomach, and duodenum (Appendix G, Table G-5).

Among the women, there were 1,847 hospitalizations and 509,265 person-years of observation in the preimmunization cohort and 268 hospitalizations and 73,947 years of observation in the postimmunization cohort. Among the men, there were 11,684 hospitalizations and 2,858,865 person-years of observation in the preimmunization cohort and 2,341 hospitalizations and 664,434 years of observation in the postimmunization cohort. Among the men, none of the adjusted rate ratios (rates before vaccination with AVA versus the rates after vaccination with AVA) were significantly greater than 1.0, and the rate ratios ranged from 0.65 to 1.02. Among the women, however, the rate of hospitalization for multiple sclerosis was significantly increased for the postimmunization cohort compared with that for the preimmunization cohort (rate ratio = 2.14, 95 percent CI = 1.14 to 4.01). When analyses were restricted to incident cases so that multiple hospitalizations of the same woman would not be counted, the adjusted rate ratio for multiple sclerosis in the postimmunization interval versus that in the preimmunization interval was no longer significantly elevated (rate ratio = 1.26; 95 percent CI = 0.50 to 3.14).

The major limitation of this sex-specific analysis is that postimmunization rates (which are, by definition, based only on those for persons who received AVA) were compared with the preimmunization rates among all active-duty personnel. The latter group includes both those who would go

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on to receive AVA and those who were never immunized with AVA. Use of this comparison group would likely reduce the magnitude of any AVA-associated hospitalizations. On the other hand, it provides a somewhat "fairer" comparison for rates of hospitalization for severe conditions, such as aplastic anemia, that would have precluded ever receiving AVA.

Interpretation of Analyses of Data from DMSS Databases The committee emphasizes that the statistically significant associations observed above are not necessarily causal associations and, indeed, most likely are not causal associations. The interpretation of data such as these requires careful attention to several important but often subtle matters. For example, upon initial review of the postexposure versus the preexposure data (i.e., the initial analyses performed to evaluate risks while controlling for the healthy soldier effect), the results appeared to suggest an elevated risk of hospitalization for diabetes mellitus after receipt of AVA. At first blush, this could be evidence that AVA uncovers cases of diabetes that otherwise might not have been detected, as has been postulated for viral infections (Robles and Eisenbarth, 2001).

However, upon closer examination, a causal link appears to be unlikely. One possibility for observing a significant increase in rates of hospitalization for diabetes would simply be chance. In fact, 27 different conditions were found to be statistically significantly associated with AVA (15 conditions with rate ratios greater than 1.0 and 12 conditions with rate ratios less than 1.0), but 42 diagnoses would be expected to be significantly different in the periods before and after vaccination with AVA purely by chance because of the large number of conditions examined. By use of a conventional p value standard of .05, one would expect 1 in 20 findings to be statistically significant just by chance. However, in this situation that explanation appears to be unlikely. In examining the results stratified by sex, they are completely consistent. Yet there is only a 1 in 400 probability (0.05×0.05) that the results could be significant for both men and women independently purely by chance.

Instead, other patterns in the data make it clear that this association is unlikely to be causal. First, the elevated risk is present to the same degree in the time period >45 days after vaccination as in the time period 0 to 45 days after vaccination. This seems unlikely, although not impossible, if the mechanism was causal.

Diabetes is a common disease that is normally treated on an outpatient basis. Data on outpatient care, however, do not appear in the detailed DMSS analyses available to the committee at the time the report was written. A selection bias may affect data on hospitalizations for diabetes. If soldiers with known diabetes who were treated as outpatients were less likely to be deployed, they would be less likely to receive AVA. The result

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would be a lower than normal rate of hospitalization for diabetes before vaccination among those who would ultimately receive AVA. Comparison of a normal rate of hospitalization for diabetes after vaccination with this lower rate before vaccination would produce the false appearance of a positive association, and this false signal would persist, regardless of whether one were examining the time period right after the vaccination (0 to 45 days) or the time period thereafter (>45 days).

How can one be confident that the true explanation is this selection bias rather than a causal connection? A separate analysis compared the rates of hospitalization for any of 843 diagnoses in the prevaccination period with the rates for those who were never vaccinated. In general, the rates of hospitalization prevaccination were lower than the rates in the group that was never vaccinated, confirming the healthy soldier effect. The adjusted rate ratios varied, but most often they were about 0.7 or 0.8. However, for diabetes the comparable adjusted rate ratio was 0.12 (95 percent CI = 0.06 to 0.24). Thus, those who received AVA were dramatically less likely to be hospitalized for diabetes than those who were never vaccinated. The normal rate of spontaneous development of diabetes after vaccination would therefore falsely appear as an increased risk. The same was true when the prevaccination rates were compared with the rates in those who never received AVA for some of the other apparent signals, such as regional enteritis (rate ratio = 0.14, 95 percent CI = 0.06 to 0.35) and other disorders of the intestine (rate ratio = 0.28, 95 percent CI = 0.12 to 0.64). For multiple sclerosis a selection bias seems even more likely, with a hospitalization rate ratio of about 0.06 for the preimmunization cohort versus those never vaccinated with AVA (based on only one preimmunization case of multiple sclerosis).

Overall, the analyses of data from DMSS were very reassuring. They indicate that exposure to AVA is not associated with a significantly increased risk for any condition of later onset that cannot be otherwise explained by biases inherent in this type of analysis. Several possible "signals" were observed, however. Signals are the earliest indication of a possible causal relationship between an exposure and a health event. These conditions include diabetes, regional enteritis, and multiple sclerosis. The committee's judgment is that these signals are probably not causally linked to exposure to AVA but most likely are due to random error or biases. However, a causal link cannot be completely excluded. Thus, these signals deserve continued surveillance; in addition, ad hoc studies are required to further explore the possible links of these signals with exposure to AVA. Such studies could involve additional analyses with data from DMSS, as well as examination of medical records to validate the diagnosis and the timing of the onset of symptoms in relation to the vaccine exposure.

The committee was impressed by the creativity and rigor of the military

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The Anthrax Vaccine: Is It Safe? Does It Work? (2002)
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professional staff working with the data in the DMSS databases and their productivity. However, the committee also counsels great caution in the use of approaches that use such data collected through automated systems for signal generation. As expected by chance alone, the rates of several diseases and conditions will predictably appear to be elevated in one group or another. Although random error and bias are likely explanations for these increases, other conclusions might also be drawn. In other words, these preliminary findings should lead to further examination of the data. The current DoD approach and organization focus on screening DMSS data for hypotheses. DoD should, however, devote more attention and resources to the evaluation of these hypotheses, as was begun in response to the committee's inquiries. As has been articulated in a set of good epidemiology practices developed for use with similar administrative and clinical data sets in civilian practice (Andrews et al., 1996), analysis of such data requires the exercise of great caution and a commitment to devote the necessary resources to explore the possible associations that might surface from such exercises. Chapter 8 discusses recommended improvements for use of DMSS data.

Thus, finding an increased rate of occurrence of one or more adverse events must be considered a signal until proper review provides an alternative explanation. Criteria for determination of which signals should be further evaluated need to be developed and routinely applied. At a minimum, a system for retrieval and review of primary medical records is required to be able to rule out coding and classification errors, to search for subtle but possibly explanatory variables that may confound an association, or to differentiate a true signal from a statistical chance event.

Finding: DMSS data are screened quarterly to identify statistically significant elevations in hospitalization and outpatient visit rate ratios associated with receipt of AVA. In this way, DMSS promises to be very useful as a tool for hypothesis generation.

Finding: The elevated rates of specific diagnoses in the various analyses of DMSS data are not unexpected per se; that is, they appear to be explicable by chance alone. The bias of selection of healthy individuals for receipt of AVA is also a likely explanation for some observed associations. Thus these elevated rates should not be automatically viewed as an indication of a causal association with the receipt of AVA. However, additional follow-up is needed.

Recommendation: AMSA staff should follow up the currently unexplained elevations in hospitalization rate ratios for certain diagnostic categories among the cohorts of AVA recipients. Studies might include

TABLE G-1 Among Service Members Receiving at Least One Dose of AVA Hospitalization Diagnoses with Rate Ratios Above 1.0, U.S. Armed Forces, Active Duty, 1998 to 2000

ICD-9-CM Code(s)	Description	Anthrax Immunization Status				Adjusted Rate Ratio	95% Confidence Intervals	
		Post		Pre				
		Number	Rate per 100,000	Number	Rate per 100,000			
193	Malignant neoplasm of thyroid gland	41	5.6	9	1.9	2.40	1.05	5.49
233	Carcinoma in situ of breast and genitourinary system	19	2.6	5	1.0	5.14	1.81	14.57
250	Diabetes mellitus	67	9.1	8	1.7	3.46	1.51	7.90
296	Affective psychoses	600	81.3	120	25.1	2.15	1.71	2.71
298	Other nonorganic psychoses	69	9.3	14	2.9	2.50	1.29	4.83
309	Adjustment reaction	1,219	165.1	403	84.3	1.38	1.20	1.59
311	Depressive disorder, not elsewhere classified	167	22.6	46	9.6	1.79	1.21	2.66
374	Other disorders of eyelids	16	2.2	7	1.5	2.71	1.05	7.00
550	Inguinal hernia	293	39.7	172	36.0	1.31	1.04	1.65
569	Other disorders of intestine	34	4.6	8	1.3	2.94	1.23	7.07
724	Other and unspecified disorders of back	108	14.6	38	7.9	1.51	1.04	2.20
726	Peripheral enthesopathies and allied syndromes	213	28.8	97	20.3	1.29	1.01	1.64
732	Osteochondropathies	38	5.1	11	2.3	2.03	1.03	3.98
808	Fracture of pelvis	53	7.2	16	3.3	1.81	1.03	3.20
823	Fracture of tibia and fibula	169	22.9	60	12.5	1.63	1.14	2.32

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TABLE G-2 Among Service Members Receiving at Least One Dose of AVA, Hospitalization Diagnoses with Rate Ratios Above 1.0, by Number of Days after Immunization, U.S. Armed Forces, Active Duty, 1998 to 2000

ICD-9-CM Code(s)	Description	Anthrax Immunization Status						Comparison*					
		Pre		0-45 days		> 45 days		0-45 / Pre			> 45 / Pre		
		Number	Rate per 100,000	Number	Rate per 100,000	Number	Rate per 100,000	Adjusted Rate Ratio	95% CI		Adjusted Rate Ratio	95% CI	
193	Malignant neoplasm of thyroid gland	9	1.68	10	6.04	31	5.41	2.88	1.12	7.37	2.16	0.90	5.17
220	Benign neoplasm of ovary	9	1.68	6	4.83	12	2.10	2.81	1.01	6.77	1.13	0.48	2.68
233	Carcinoma in situ of breast and genitourinary system	5	1.05	5	3.02	14	2.44	4.12	1.17	14.49	5.85	1.95	17.58
250	Diabetes mellitus	8	1.67	13	7.85	54	9.43	3.49	1.39	8.79	3.44	1.47	8.06
296	Affective psychoses	120	25.10	102	61.56	498	86.96	1.84	1.39	2.43	2.31	1.82	2.94
298	Other nonorganic psychoses	14	2.93	9	5.43	60	10.48	1.52	0.64	3.62	3.08	1.55	6.13
304	Drug dependence	6	1.25	2	1.21	33	5.76	.	.	.	3.06	1.08	8.66
309	Adjustment reaction	403	84.29	258	155.72	961	167.80	1.37	1.16	1.62	1.38	1.19	1.61
311	Depressive disorder, not elsewhere classified	46	9.62	35	21.12	132	23.05	1.78	1.11	2.84	1.80	1.19	2.72
312	Disturbance of conduct, not elsewhere classified	6	1.25	0	0.00	12	2.10	.	.	.	1.41	1.41	1.41
414	Other forms of chronic ischemic heart disease	18	3.76	20	12.07	81	14.14	2.15	1.09	4.23	1.65	0.89	3.07
429	Ill-defined descriptions and complications of heart dises	6	1.25	0	0.00	12	2.10	.	.	.	1.32	1.32	1.32
451	Phlebitis and thrombophlebitis	5	1.05	0	0.00	12	2.10	.	.	.	1.58	1.58	1.58
470	Deviated nasal septum	45	9.41	23	13.88	90	15.72	1.19	0.72	1.97	1.47	1.02	2.11
493	Asthma	41	8.58	30	18.11	64	11.18	1.83	1.14	2.93	1.10	0.74	1.64
541	Appendicitis, unqualified	47	9.83	19	11.47	77	13.45	1.15	0.68	1.97	1.46	1.01	2.11
550	Inguinal hernia	172	35.98	76	45.87	217	37.89	1.24	0.93	1.65	1.36	1.05	1.76
569	Other disorders of intestine	6	1.25	10	6.04	24	4.19	4.18	1.51	11.49	2.61	1.06	6.44
598	Urethral stricture	22	5.18	8	5.38	51	9.89	0.96	0.43	2.16	1.66	1.00	2.75
622	Noninflammatory disorders of cervix	15	28.20	22	129.54	48	84.28	2.64	1.30	5.35	1.55	0.78	3.09
724	Other and unspecified disorders of back	38	7.95	19	11.47	89	15.54	1.25	0.72	2.18	1.59	1.08	2.33
733	Other disorders of bone and cartilage	95	19.87	45	27.16	194	33.87	1.12	0.77	1.62	1.45	1.06	1.96
735	Acquired deformities of toe	34	7.11	20	12.07	83	14.49	1.15	0.68	2.01	1.58	1.06	2.37
808	Fracture of pelvis	16	3.35	11	6.64	42	7.33	1.66	0.77	3.60	1.86	1.04	3.34
823	Fracture of tibia and fibula	60	12.55	36	21.73	133	23.22	1.53	0.99	2.37	1.68	1.15	2.46
865	Injury to spleen	9	1.88	10	6.04	19	3.32	2.83	1.15	6.99	1.61	0.72	3.58
999	Complications of medical care, not elsewhere classified	7	1.46	5	3.02	5	0.87	3.70	1.05	13.04	1.25	0.30	5.11

TABLE G-3 Among Service Members Receiving at Least One Dose of AVA, Hospitalization Diagnoses with Rate Ratios Above 1.0, by Number of Doses After Immunization, U.S. Armed Forces, Active Duty, 1998 to 2000

ICD-9-CM	Description	Anthrax Immunization Status						Comparison			
		Pre		1 to 3 doses		4 or more doses		1 to 3 doses/Pre		4 or more/Pre	
		Number	Rate/100,000	Number	Rate/100,000	Number	Rate/100,000	Adjusted Rate ratio	95%CI	Adjusted Rate ratio	95%CI
193	Malignant neoplasm of thyroid gland	9	1.88	12	6.51	29	5.23	2.55	0.94-6.94	2.35	1.01-5.48
225	Benign neoplasm of brain and other parts of nervous system	6	1.25	8	4.34	6	1.08	2.99	1.02-8.77	0.70	0.22-2.19
250	Diabetes mellitus	8	1.67	24	13.02	43	7.76	4.98	2.02-12.25	3.05	1.31-7.09
296	Affective psychoses	120	25.10	229	124.27	371	66.95	3.65	2.81-4.74	1.79	1.42-2.27
298	Other nonorganic psychoses	14	2.93	26	14.11	43	7.76	4.08	1.92-8.68	2.11	1.07-4.18
300	Neurotic disorders	69	14.43	70	37.99	101	18.23	2.20	1.46-3.30	0.92	0.64-1.32
301	Personality disorders	64	13.39	115	62.41	81	14.62	1.95	1.32-2.87	0.69	0.46-1.02
304	Drug dependence	6	1.25	13	7.05	22	3.97	4.20	1.37-12.91	1.81	0.64-5.07
309	Adjustment reaction	403	84.29	460	249.63	759	136.98	2.28	1.94-2.69	1.16	1.00-1.34
311	Depressive disorder, not elsewhere classified	46	9.62	49	26.59	118	21.30	2.60	1.62-4.20	1.63	1.09-2.44
346	Migraine	36	7.53	30	16.28	46	8.30	1.82	1.12-2.98	0.90	0.58-1.40

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